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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,317	12/20/1999	RANDOLPH NOELLE	012712-813	2231

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	14

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/467317	Applicant(s) NOELLE
	Examiner GAMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 6/9/03

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 42-81

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed. 69, 61, 63, 64, 66, 67, 69, 70, 71, 73, 75, 77-79, 81-81

6)☑ Claim(s) _____ is/are rejected. 42-59, 62, 65, 68, 71, 74, 76, 80

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 14

DETAILED ACTION

1. Applicant's amendment, filed 6/9/03 (Paper No. 11), has been entered.
Claims 43, 45, 47-56 have been amended.
Claims 59-82 have been added.

Claims 42-82 are pending.

Claims 1-41 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendment, filed 6/9/03.
The rejections of record can be found in previous Office Action (Paper No. 10).

3. Applicant's provision of a sub specification filed 6/9/03 is acknowledged. However, the only copy of the substitute specification is a marked-up copy of the substitute specification.

Therefore, a new substitute specification , which must be accompanied by a statement that it contains no new matter, is required.. Such statement must be a verified statement if made by a person not registered to practice before the Office.

The examiner apologizes for any inconvenience in this matter.

4. Applicant's communication, filed 6/9/03, has placed this application in compliance with the Sequence Rules.

5. Formal drawings submitted 6/9/03 comply with 37 CFR 1.84.

6. The previous rejection under 35 U.S.C. § 112, first paragraph, written description / new matter, with respect to the recitation of "A method for inhibiting ... to a protein specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC No. HB 11048" has been withdrawn in view of applicant's amended claim 48, filed 6/9/03.

7. New Matter:
Claims 42, 43, 48, 49, 54-58 and newly added 59, 62, 65, 68, 71, 74, 76, 80 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:
"A method for inhibiting a humoral immune response ...." .

Applicant's arguments filed 6/9/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant relies upon the The Illustrated Dictionary of Immunology (Cruse & Lewis, CRC Press, Boca Raton, 1995) to define humoral immunity as "immunity attributable to specific immunoglobulin antibody and present in the blood plasma, lymph, other body fluids or tissues ... Antibodies that are the messengers of humoral immunity are derived from B cells." Applicant further submits that the definition makes clear that humoral immunity requires antibodies produced by B cell activation, as disclosed in the instant application and may also include involvement of T cells, as suggested by the examiners. In addition, applicant notes that the instant specification discloses that the compositions of the invention are relevant to the treatment of humoral immunity disorders (see pages 19-21 of the instant specification).

As pointed out previously, applicant's amendment, filed 12/20/99, directed written support of the newly claims to pages 17-19, pages 28-31 and certain original claims for "humoral immunity".

Obviousness is not the standard for the addition new limitations to the disclosure as filed.
It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

While the instant specification as filed, including the Uses of CD40CR on pages 19-21 in addition to the cited sections by applicant support methods of inhibiting B cell activation and immunoglobulin production, there appears insufficient written description in the specification as filed for "methods for inhibiting humoral immunity".

Again, the Illustrated Dictionary of Immunology (Cruse and Lewis, CRC Press, Boca Raton, 1995) discloses that humoral immunity is attributable to specific immunoglobulin antibody, which can result in both beneficial and deleterious reactions and is not clearly distinguished from cellular or T cell immunity (see page 143). Humoral immunity can comprise various cell types and mediators associated with the immune response. Humoral immunity is not limited to B cell activation and immunoglobulin production, as disclosed by the specification as filed.

The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06

8. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 43, 47, 49, 51, 53-58 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

Applicant's arguments, filed 6/9/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that the recitation of "a 39 kD protein located on T helper cell membranes" supported by the application as filed (e.g. page 2, lines 27 - page 3, line 4 of the instant specification) as well as the functional properties of a CD40CR protein, including its ability to bind CD40 B-cell antigen and to stimulate B cell cycle entry, proliferation and differentiation", satisfies the written description of a CD40CR protein.

In addition, applicant submits that at the time of filing of the instant application, CD40CR had been described in several species, including Hollenbaugh et al. (EMBO J 11: 4313-4321, 1992) and Spriggs et al. (J. Exp. Med 176: 1543-1550 (1992).

Neither Hollenbaugh et al. (EMBO J 11: 4313-4321, 1992) nor Spriggs et al. (J. Exp. Med 176: 1543-1550 (1992) is disclosed in the application as filed.

Further, applicant asserts the art makes clear that a skilled artisan would not understand the term "CD40CR" and following a review of the disclosure of the instant application, would conclude that the applicant was in possession of the necessary common attributes possessed by antibodies that bind to CD40CR.

There is insufficient written description encompassing "CD40CR" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of "CD40CR" are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is relying upon certain biological activities and the disclosure of the limited representative species of a mouse CD40CR (e.g. see Sections 6.2.3 and 6.2.4 as well as Figures 4- 6) to support an entire genus of CD40CR as it reads on mammalian, including human CD40CR. The instant invention encompasses any CD40CR as a target of the instant methods, yet the instant specification does not provide sufficient written description as to the structural features of said CD40CR and the correlation between the chemical structure and the function of the genus of CD40CRs. Applicant appears to rely upon the disclosure of a limited example of a mouse CD40CR.

While the specification discloses a starting point for screening or testing for molecules that have the characteristics of a 39 kD protein on helper T cells membranes, which binds to CD40 B cell antigen and stimulates B cell cycle entry, the instant disclosure does not set forth any procedures that will necessarily lead to discovery for such molecules broadly encompassed by the claimed invention and it does not identify a sufficient number of representative members of such molecules (e.g. human CD40 ligand). The application does little more than describe the desired function of the claimed genus of CD40CR molecules broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

While Section 7 of the instant specification discloses binding of CD40Ig to human T cell lines, there is no isolation nor written description of the human CD40CR.

Furthermore, there is insufficient written description of the genus of CD40CR(s), including as it reads on mammalian as well as human CD40CR.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Further, Skolnick et al. (Trends in Biotech., 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the mouse CD40CR disclosed as filed does not appear to provide sufficient written description of a genus of distinct molecules of "CD40CR(s), encompassed by the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "CD40CR(s); one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant's arguments are not found persuasive.

11. The previous rejections under 35 U.S.C. § 112, second paragraph, have been withdrawn in view of applicant's amended claims, filed 6/9/03.

12. Applicant's Request for Interference Pursuant to 37 CFR §§1.607(a) and 1.609(a) is acknowledged.

Applicant's comments concerning expediting the prosecution of the instant application are acknowledged.

However, the claims are not deemed allowable for the reasons set forth of record and herein.

In addition, a Decision of the Board of Appeals and Interferences, 08/742,480 v. 5,474,771, Patent Interference No. 104,415, October 19, 2001, wherein parent application USSN 08/742,480 was one of the parties is made of record.

13. Claims 43, 45, 47, 49, 51 and 53-58 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lederman et al. (U.S. Patent No. 5,993,816) (see entire document). Lederman et al. teach methods of inhibiting humoral immune responses, including B cell activation and immunoglobulin production by 5c8-specific antibodies (e.g., see Background of the Invention, columns 10-11, and Example 7 on columns 23-27), including antibody fragments, chimeric, humanized and human antibodies as well as antibody conjugates (columns 6-8) (also, see Claims). The 5c8 specificity is the equivalent of the human CD40 ligand or CD40CR, as recited in the instant claims. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to inhibit humoral immune responses, B cell activation and immunoglobulin production by 5c8-specific antibodies.

14. Claims 42-58 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lederman et al. (U.S. Patent No. 5,993,816) in view of Armitage et al. (U.S. Patent No. 5,961,974).

Lederman et al. teach methods of inhibiting humoral immune responses, including B cell activation and immunoglobulin production by helper T cell-specific antibodies, including the 5c8-specific antibodies (e.g., see Background of the Invention, columns 10-11, and Example 7 on columns 23-27), including antibody fragments, chimeric, humanized and human antibodies as well as antibody conjugates (columns 6-8) (also, see Claims). The 5c8 specificity is the equivalent of the human CD40 ligand or CD40CR, as recited in the instant claims.

Lederman et al. differs from the claimed methods by not disclosing the protein specifically recognized by the MR1 antibody which binds the mouse CD40 ligand (CD40L).

Armitage et al. teach the mouse and human CD40L on T cells, wherein CD40L is involved in T - B cell interactions, which are associated with B cell proliferation and differentiation resulting in immunoglobulin secretion (See entire document, including Detailed Description of the Invention and Examples 1-13). Armitage et al. teach the use of antagonists of CD40:CD40L interactions which prevent CD40L binding to CD40 sites on B cells and other target cells, which can be used in therapeutic modalities (see Detailed Description of the Invention) (e.g. columns 10-11, including overlapping paragraph, columns 14-17; column 21)

Given the ability of helper T cell 5C8-/CD40L-specific antibodies, as taught by Lederman et al. OR the ability of various CD40 antagonists, as taught by Armitage et al. to inhibit various immune responses, including T helper cell-mediated immune responses, including humoral responses; one of ordinary skill in the art at the time the invention was made would have been motivated to generate antibody antagonists, including antibody fragments, chimeric, humanized, human antibodies as well as antibody conjugates, as known by the ordinary artisan and taught by Lederman et al. to the mouse and human CD40L taught by Armitage et al. to similarly target T helper cells in order to inhibit humoral responses, B cell proliferation and immunoglobulin production. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 42-53, (54) and 55 (and 56-58) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lederman et al. (U.S. Patent No. 5,993,816)
or over Lederman et al. (U.S. Patent No. 5,993,816) in view of Armitage et al. (U.S. Patent No. 5,961,974) in view of the art known use of antibody conjugates in inhibiting immune responses by the ordinary artisan at the time the invention was made, as evidenced by Ultee et al. (U.S. Patent No. 4,937,183).

Lederman et al. and Lederman et al. in view of Armitage et al. are taught above and differ from the claimed methods by not disclosing all of the well known antibody conjugates recited in claim 55.

A wide variety of antibody conjugates for inhibiting immune responses were well known and practiced by the ordinary artisan at the time the invention was made, including those recited in claim 55, as evidenced by Ultee et al. (See entire document, including Section 5.2, particularly columns 7-8, overlapping paragraph, Sections 5.3, 5.4, 5.5).

Given the well known use of a variety of antibody conjugates employed in therapeutic modalities to inhibit immune responses, it would have been obvious to one of ordinary skill in the art to conjugate either human or mouse CD40L-specific antibodies to inhibit humoral immune responses, including the inhibition of B cell activation and immunoglobulin production, as taught by Lederman et al. or Lederman et al. in view of Armitage et al. as taught above, at the time the invention was made. The various conjugates were well known to provide additional immunosuppressant properties for therapeutic antibodies that target cells of interest at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Newly added claims 59-82 which employ the MR1 antibody produced by the hybridoma having the ATCC Accession No. HB 11048 appear free of the prior art. Due to high polymorphism of antibodies, the MR1 antibody produced by the ATCC Accession No. HB 11048 is deemed structurally distinct on the primary amino acid basis and therefore free from the prior art.

Claims 60, 61, 63, 64, 66, 67, 69, 70, 72, 73, 75, 77-79 and 81-82 are deemed allowable.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
November 17, 2003